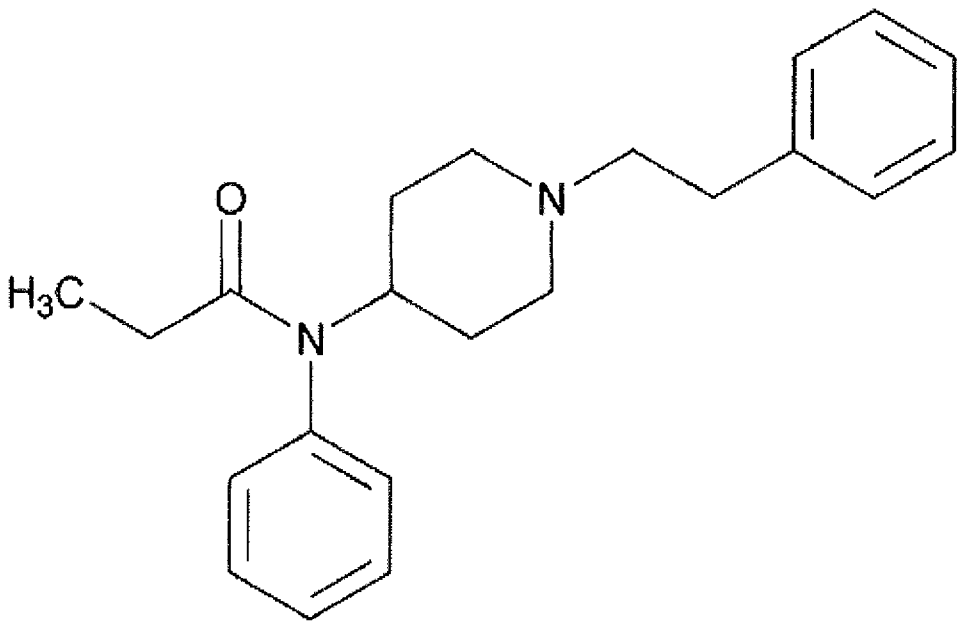
Fentanyl

(fen' ta nil).



USP Image 3D Image

$C_{22}H_{28}N_2O$ 336.47

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl];
N-(1-Phenethylpiperidin-4-yl)-*N*-phenylpropionamide [437-38-7].

DEFINITION

Fentanyl contains NLT 98.0% and NMT 102.0% of the labeled amount of $C_{22}H_{28}N_2O$, calculated on the dried basis. [**CAUTION**—Great care should be taken to prevent inhaling particles of Fentanyl and exposing the skin to it.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** 〈197K〉
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Solution A: Add 3 mL of triethylamine to about 950 mL of water in a 1000-mL volumetric flask, adjust with perchloric acid to a pH of 2.62 ± 0.02, and dilute with water to volume.

Solution B: Acetonitrile

Diluent: *Solution A* and *Solution B* (9:1)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
3.5	85	15
5.1	82	18
7.6	72	28
11.5	63	37
15	40	60
19	40	60
20	90	10
25	90	10

System suitability stock solution: 0.4 mg/mL of USP Fentanyl Related Compound A RS, and about 0.1 mg/mL each of USP Fentanyl Related Compound B RS, USP Fentanyl Related Compound D RS, USP Fentanyl Related Compound E RS, and USP Fentanyl Related Compound G RS, prepared by dissolving in a suitable volumetric flask 50% filled with acetonitrile and diluting with water to volume

System suitability solution: 0.3 µg/mL each of USP Fentanyl Related Compound B RS, USP Fentanyl Related Compound D RS, USP Fentanyl Related Compound G RS, and USP Fentanyl Related Compound E RS; 1.3 µg/mL of USP Fentanyl Related Compound A RS; and 100 µg/mL of USP Fentanyl RS, prepared by diluting an appropriate amount of *System suitability stock solution* in *Diluent*

Standard stock solution: 1 mg/mL of USP Fentanyl RS dissolved in acetonitrile in a suitable volumetric flask, (40% of the flask volume), and diluted with water to volume

Standard solution: 0.1 mg/mL of USP Fentanyl RS from the *Standard stock solution* in *Diluent*

Sample stock solution: Transfer 100 mg of Fentanyl to a 100-mL volumetric flask, add 25 mL of acetonitrile, dissolve by shaking, and dilute with *Diluent* to volume.

Sample solution: 0.1 mg/mL of Fentanyl from the *Sample stock solution* in *Diluent*

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 206 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L7

Column temperature: 35°

Flow rate: 1 mL/min

Injection size: 30 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Tailing factor: NLT 0.5 and NMT 2.0, fentanyl and fentanyl related compound peaks

Resolution: NLT 1.2 between fentanyl and fentanyl related compound E peaks

Relative standard deviation: NMT 0.7% for fentanyl and NMT 10% for fentanyl related compounds

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{22}H_{28}N_2O$ in the portion of Fentanyl taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of Fentanyl from the *Sample solution*

r_S = peak response of fentanyl from the *Standard solution*

C_S = concentration of fentanyl in the *Standard solution* (mg/mL)

C_U = concentration of Fentanyl in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

Inorganic Impurities

- RESIDUE ON IGNITION ⟨ 281 ⟩: NMT 0.5%
- HEAVY METALS, *Method II* ⟨ 231 ⟩: 20 ppm

Organic Impurities

- PROCEDURE

Solution A, Solution B, Diluent, System suitability solution, Sample stock solution, and **Chromatographic system:** Proceed as directed in the *Assay.*

Standard stock solution: 0.1 mg/mL of USP Fentanyl Related Compound E RS in a suitable volumetric flask, dissolve in acetonitrile (50% of the flask volume), and dilute with water to volume. Dilute an aliquot with *Diluent* to obtain a concentration of about 1.2 µg/mL.

Standard solution: 0.024 µg/mL of USP Fentanyl Related Compound E RS from the *Standard stock solution* in *Diluent*

Sample solution: 250 µg/mL of Fentanyl from the *Sample stock solution* in *Diluent*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Fentanyl taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of fentanyl related compound E from the *Standard solution*

C_S = concentration of USP Fentanyl Related Compound E RS in the *Standard solution* (µg/mL)

C_U = concentration of Fentanyl in the *Sample solution* (ug/mL)

F = relative response factor of the fentanyl related compounds (see *Impurity Table 1*)

Acceptance criteria

[NOTE—Identify fentanyl related compound C and fentanyl related compound F by using the relative retention times provided in *Impurity Table 1*. Identify the other impurity peaks in the sample by comparing them to those in the *System suitability solution*.]

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time[a]	Relative Response Factor[b]	Acceptance Criteria, NMT (%)
Fentanyl related compound B[c]	0.28	0.67	0.015
Fentanyl related compound C[d]	0.56	0.67	0.25
Fentanyl related compound D[e]	0.86	0.97	0.015
Fentanyl related compound G[f]	0.89	0.82	0.25
Fentanyl related compound F[g]	0.92	0.75	0.25
Fentanyl related compound E[h]	0.98	1.00	0.015
Fentanyl	1.00	—	—
Fentanyl related compound A[i]	1.26	0.55	0.25
Individual unspecified impurities	—	—	0.10

[a] The relative retention time is calculated based on fentanyl.

[b] The relative response factor (RRF) is calculated based on fentanyl related compound E.
[c] 4-Anilinopiperidine.
[d] *N*-Phenyl-*N*-(4-piperidinyl)propanamide.
[e] *N*-Phenyl-1-(phenylmethyl)-4-piperidinamine.
[f] *N*-Phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]acetanilide hydrochloride, or acetyl fentanyl.
[g] *N*-(1-Benzyl-4-piperidinyl)propionanilide.
[h] *N*-Phenyl-1-(2-phenylethyl)-4-piperidinamine.
[i] (2-Bromoethyl)benzene.

SPECIFIC TESTS

- **LOSS ON DRYING** ⟨ 731 ⟩**:** Dry a sample in vacuum at 60° for 2 h: it loses NMT 0.5% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tightly closed, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.
- **USP REFERENCE STANDARDS** ⟨ 11 ⟩

  USP Fentanyl RS
  USP Fentanyl Related Compound A RS
  USP Fentanyl Related Compound B RS
  USP Fentanyl Related Compound C RS
  USP Fentanyl Related Compound D RS
  USP Fentanyl Related Compound E RS
  USP Fentanyl Related Compound F RS
  USP Fentanyl Related Compound G RS

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
Monograph	Clydewyn M. Anthony, Ph.D. Senior Scientific Liaison 1-301-816-8139	(SM22010) Monographs - Small Molecules 2
Reference Standards	RS Technical Services 1-301-816-8129 rstech@usp.org	

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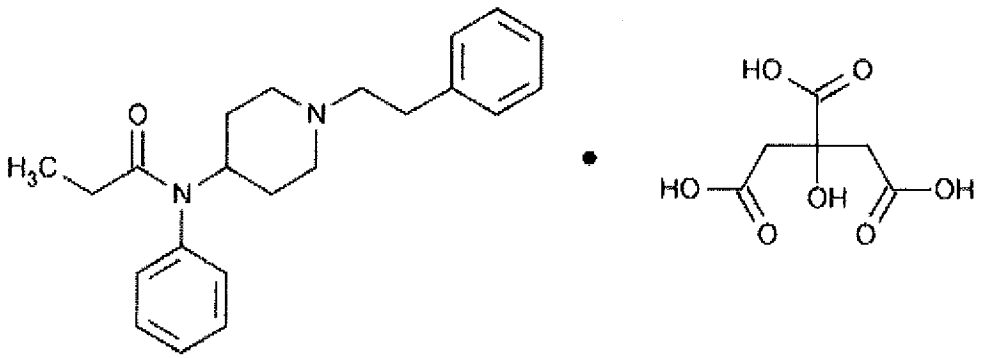
Chromatographic Column—

FENTANYL

Chromatographic columns text is not derived from, and not part of, USP 34 or NF 29.

Fentanyl Citrate

(fen' ta nil sit' rate).



USP Image 3D Image

$C_{22}H_{28}N_2O \cdot C_6H_8O_7$ 528.59

Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

N-(1-Phenethyl-4-piperidyl)propionanilide citrate (1:1) [990-73-8].

» Fentanyl Citrate contains not less than 98.0 percent and not more than 102.0 percent of $C_{22}H_{28}N_2O \cdot C_6H_8O_7$, calculated on the dried basis.

[**CAUTION**—*Great care should be taken to prevent inhaling particles of Fentanyl Citrate and exposing the skin to it.*]

Packaging and storage— Preserve in well-closed, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

USP REFERENCE STANDARDS ⟨ 11 ⟩—

USP Fentanyl Citrate RS

Identification—

A: ***INFRARED ABSORPTION*** ⟨ 197K ⟩.

B: ***ULTRAVIOLET ABSORPTION*** ⟨ 197U ⟩—

Solution: 500 µg per mL.

Medium: dilute hydrochloric acid in methanol (1 in 10).

LOSS ON DRYING ⟨ 731 ⟩— Dry it in vacuum at 60° for 2 hours: it loses not more than 0.5% of its weight.

RESIDUE ON IGNITION ⟨ 281 ⟩: not more than 0.5%.

HEAVY METALS, *Method II* ⟨231⟩: 0.002%.

ORDINARY IMPURITIES ⟨466⟩ —

Test solution: a mixture of chloroform and methanol (4:1).

Standard solution: a mixture of chloroform and methanol (4:1) except to eliminate the 0.01 mg per mL solution and add a 0.02 mg per mL solution.

Procedure— Use a thin-layer chromatographic plate coated with chromatographic silica gel with a calcium sulfate binder.

Eluant: a mixture of chloroform, methanol, and formic acid (85:10:5).

Visualization: 3.

Assay— Dissolve about 500 mg of Fentanyl Citrate, accurately weighed, in 30 mL of glacial acetic acid. Add 3 drops of *p*-naphtholbenzein TS, and titrate with 0.05 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.05 N perchloric acid is equivalent to 26.43 mg of $C_{22}H_{28}N_2O \cdot C_6H_8O_7$.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
Monograph	Clydewyn M. Anthony, Ph.D. Senior Scientific Liaison 1-301-816-8139	(SM22010) Monographs - Small Molecules 2
Reference Standards	RS Technical Services 1-301-816-8129 rstech@usp.org	

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Fentanyl Citrate Injection

» Fentanyl Citrate Injection is a sterile solution of Fentanyl Citrate in Water for Injection. It contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fentanyl ($C_{22}H_{28}N_2O$), present as the citrate.

Packaging and storage— Preserve in single-dose containers, preferably of Type I glass, protected from light.

USP REFERENCE STANDARDS ⟨ 11 ⟩ —

USP Endotoxin RS

USP Fentanyl Citrate RS

Identification— The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

BACTERIAL ENDOTOXINS ⟨ 85 ⟩ — It contains not more than 50.0 USP Endotoxin Units per mg.

pH ⟨ 791 ⟩ : between 4.0 and 7.5.

Other requirements— It meets the requirements under *Injections* ⟨ 1 ⟩ .

Assay—

Mobile phase— Prepare a filtered and degassed mixture containing 4 volumes of ammonium acetate solution (1 in 100) and 6 volumes of a mixture of methanol, acetonitrile, and glacial acetic acid (400:200:0.6). Adjust this solution to a pH of 6.6 ± 0.1 by the dropwise addition of glacial acetic acid, and make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨ 621 ⟩), to obtain a retention time of about 5 minutes for the fentanyl peak.

Standard preparation— Dissolve an accurately weighed quantity of USP Fentanyl Citrate RS in water, and quantitatively dilute with water to obtain a solution having a known concentration of about 80 µg per mL.

Assay preparation— If necessary, dilute the Injection with water so that each mL contains the equivalent of about 50 µg of fentanyl.

Chromatographic system (see *Chromatography* ⟨ 621 ⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation*, and record

the peak response as directed for *Procedure:* the tailing factor for the fentanyl peak is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of fentanyl ($C_{22}H_{28}N_3O$) in each mL of the Injection taken by the formula:

$$(336.48 / 528.59)CD(r_U / r_S)$$

in which 336.48 and 528.59 are the molecular weights of fentanyl and fentanyl citrate, respectively; *C* is the concentration, in µg per mL, of USP Fentanyl Citrate RS in the *Standard preparation; D* is the dilution factor used to obtain the *Assay preparation;* and r_U and r_S are the peak responses for the fentanyl peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Auxiliary Information— Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
Monograph	Clydewyn M. Anthony, Ph.D. Senior Scientific Liaison 1-301-816-8139	(SM22010) Monographs - Small Molecules 2
Reference Standards	RS Technical Services 1-301-816-8129 rstech@usp.org	
⟨ 85 ⟩	Radhakrishna S Tirumalai, Ph.D. Principal Scientific Liaison 1-301-816-8339	(GCM2010) General Chapters - Microbiology

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Chromatographic Column—

FENTANYL CITRATE INJECTION

Chromatographic columns text is not derived from, and not part of, USP 34 or NF 29.